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Ritscher-Schinzel (3C) Syndrome: Documentation of the Phenotype

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Ritscher-Schinzel syndrome or 3C (craniocerebello-cardiac) syndrome is characterized by cardiac defects, cerebellar vermis hypoplasia, and cranial defects. Nineteen cases were reported previously; however, the full spectrum of this disorder has not been determined. We have evaluated two unrelated males with this condition. Both had defects of the endocardial cushion and vermis hypoplasia with hypotonia. In addition, both had hypospadias, a previously undescribed finding of this disorder.

Review of the previously reported cases and those described herein demonstrate: 1) Although varying degrees of vermis hypoplasia are accompanied by hypotonia, delayed gross motor function improves with advancing age leaving speech delay as the major neurodevelopmental handicap. 2) Two different types of cardiac anomalies occur: defects of the endocardial cushion ranging from anomalies of the mitral or tricuspid valves to complete AV canal, and/or conotruncal defects. 3) Postnatal growth deficiency was seen in most patients in whom longitudinal information was available.

In our review of patients with vermis hypoplasia we ascertained a patient diagnosed as having "Joubert syndrome" who had most findings of the Ritscher-Schinzel syndrome and several other patients with "Dandy-Walker syndrome" who likely have had Ritscher-Schinzel syndrome, suggesting that Ritscher-Schinzel syndrome is more common than has been appreciated. Careful search for the subtle facial changes characteristic of this disorder as well as coloboma, cleft palate/bifid uvula, short neck, syndactyly, and hypoplasia of the nails is warranted when evaluating children with Dandy-Walker malformation with or without clinical signs of Joubert syndrome. Am. J. Med. Genet. 68:421–427, 1997.

KEY WORDS: Dandy-Walker malformation; Joubert syndrome; endocardial cushion defect; hypospadias; malrotation of the gut

INTRODUCTION

In 1987 Ritscher et al. reported on two sisters with similar craniofacial anomalies, one of whom had a complete common atrioventricular canal and Dandy-Walker variant while the other had a partial atrioventricular canal and a Dandy-Walker malformation. Subsequently Verloes et al. reported a third child affected with this disorder which they referred to as 3C (craniocerebello-cardiac) dysplasia [1989]. Since then, 19 cases referred to as either Ritscher-Schinzel or 3C syndrome have been reported [Mims and Say, 1989; Gurrieri and Neri, 1992; Hoo et al., 1994; Wörle et al., 1994; Quintana et al., 1994; Digilio et al., 1995; Marles et al., 1995, Saraiva et al., 1995]. Here we describe two additional male patients with this disorder to further delineate the phenotype of this disorder.

CLINICAL REPORTS

Patient 1

TJ, a boy, was the product of a 38 week pregnancy to a 27-year-old white primigravid woman and her 29-year-old husband. Fetal activity began at 18 weeks of gestation. Ultrasound examination at 19 weeks showed a possible Dandy-Walker cyst. Delivery was from a vertex position. Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Birth weight was 2.11 kg (3rd centile) and length was 47 cm (25–50th centile). Head circumference (OFC) was 33 cm (50th centile). At birth the presence of a Dandy-Walker malformation was confirmed and hypospadias with chordee was noted. At age 2 weeks, a heart murmur was noted and an ultrasound examination showed complete atrioventricular canal,

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for which corrective surgery was performed at 5 months. At 4 months fundoplication was performed for gastroesophageal reflux. Subsequently, he was noted to have malrotation of the gut. At 8 months a ventriculoperitoneal shunt was placed because of hydrocephalus. He developed head control at 8 months and sat without support at 1 year. Hypotonia which had been present since birth gradually improved. He cruised at 15 months and walked at 20 months. At 15–16 months, he spoke single words and by 23 months he put two words together and was extremely outgoing.

Findings at 25 months of age included a weight of 9.74 kg (3rd centile), length of 78.5 cm (3rd centile), and an OFC of 46 cm (10–25th centile) (Fig. 1). He had a prominent forehead and left occipital plagiocephaly. Innercanthal distance was 3.1 cm (97th centile). The palpebral fissures, which were down-slanting, measured 2.1 cm. The ocular fundi were normal. He had recently developed an esotropia. Except for repaired hypospadias, genitalia were normal. The hands measured 9.5 cm (3–25th centile). The fifth finger nails were hypoplastic and a cavernous hemangioma was present on the dorsum of the right hand. The family history was unremarkable and there was no parental consanguinity.

Patient 2

JB, a male, was the product of a term pregnancy to a 38-year-old, gravida 8, para 5 SAB 3 woman and her 43-year-old husband. Ultrasound findings at 20 weeks were normal. Delivery was by elective cesarean section due to breech position. Birth weight was 3.47 kg (75th centile) and OFC was 37.5 cm (90th centile). Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Mild respiratory difficulty required oxygen therapy for several hours. Dandy-Walker malformation with enlarged ventricles was diagnosed by CT scan. On the third day, a soft systolic murmur was audible. Echocardiography demonstrated a large ostium secundum atrial septal defect, small ventricular septal defect, and a "dysplastic" tricuspid valve. Chromosomes were normal. Physical findings at one month included length of 53 cm (25–50th centile) weight of 4 kg (25–50th centile) and OFC of 39 cm (75th centile), a large anterior fontanelle, two posterior hair whorls and a prominent nevus flammeus of the glabella, innercanthal distance of 2.5 cm (90th centile), and downslanting of the palpebral fissures. Ears were retroverted and apparently low-set. Redundant posterior nuchal skin was present. A supernumerary nipple was present on the left side. There was mild cutaneous finger syndactyly. He had a bifid uvula. There were hypospadias, chordee, and a cleft of the scrotum with a prominent median raphé. Truncal tone was decreased and head control was delayed and there were brisk deep tendon reflexes, jerky eye movements, and several prolonged and striking episodes of hyperpnea during the first months of life. Fundi were normal. An ERG was normal. At age 7 months, he transferred objects from hand to hand but could not sit without support. He had failure to thrive. At 16 months he started to walk, spoke two words with meaning and was extremely sociable (Fig. 2). At 7 months an MRI showed cerebellar vermis hypoplasia, a prominent supravermian cistern, and thinning of the corpus callosum. Mild enlargement of the lateral ventricles and the third ventricle was also present. At 15 months he underwent repair of his large ostium secundum ASD and his perimembranous VSD was closed by apposition of overlying tricuspid valve septal leaflet tissue. Following surgery his growth improved although he continues to have intermittent gagging and avoids chewing solid foods. He has mild gastroesophageal reflux.

DISCUSSION

Evaluation of the two patients and of those from the literature permits a more complete delineation of the phenotype of the Ritscher-Schinzel (3C) syndrome.

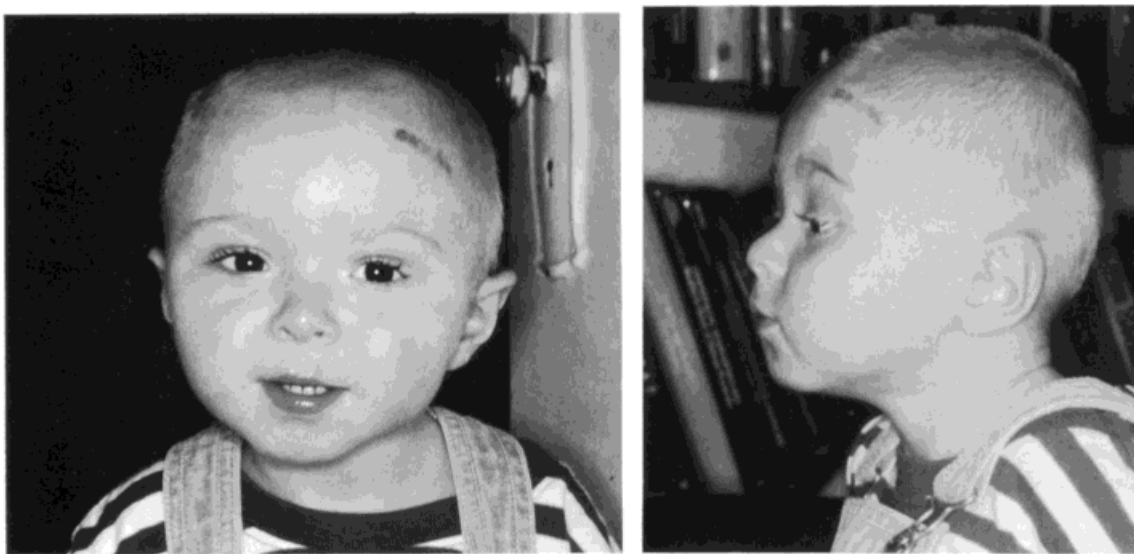

Fig. 1. Patient 1 at age 25 months.

Fig. 2. Patient 2 at age 16 months.

Findings in 16 affected children are summarized in Table I and are further described below. Prior to the report by Marles et al. [1995] of eight native Canadian children, cerebellar hypoplasia and cardiac defects had been considered invariable in this disorder. However, based on one patient with an affected sib from that report who had a complete AV canal but lacked cerebellar hypoplasia, it is likely that no single defect is invariable. In five of the remaining eight patients of that report we were unsure of the diagnosis because neither a characteristic heart defect nor cerebellar hypoplasia was present and a family history was lacking. Thus, only three of the eight patients reported by Marles et al. are included in Table I.

In all nine patients in whom development was described adequately, gross motor delay was present and was most likely related to hypotonia associated with cerebellar defect. Among the four cases for which adequate data were available, the mean age at walking was 19 months. Given the role played by the cerebellar vermis in speech development, it is not surprising that speech is generally more affected than cognitive development. Of the seven children who were 2 years old or older, two began using single words with meaning at 16 months, one had the language development of a 1 year old at 2 years of age, two had the language development of a 1 year old at a chronologic age of 3 years, and one child could follow simple instructions but did not talk at 30 months of age. Limited information is available relative to intellectual performance. The oldest patient described is a 6-year-old girl who was described as having "psychomotor retardation at the 4.5 to 5 year old level." Of particular significance, although the two patients reported herein had significant gross motor delay, marked improvement occurred. By age 2 years both children could walk, put two words together with meaning and were outgoing and sociable.

The mean birth weight of the 11 babies who were born at term was 3.08 kg. Postnatal growth deficiency was noted in 9 out of 11 patients whose growth was recorded on at least two separate occasions. Linear growth rate in those patients averaged 57% of normal, while average rate of weight gain averaged 45% of normal. The extent to which heart failure contributes to the postnatal growth deficiency is unknown. There was significant evidence of feeding dysfunction and gastroesophageal reflux in the two patients reported here.

Although the term Dandy-Walker malformation or Dandy-Walker variant was used to describe the brain defect in most patients, there was considerable variability in the defects described. Cerebellar vermis hypoplasia was specifically mentioned in 12 patients while in 2, vermis hypoplasia was suggested indirectly by enlargement of the fourth ventricle and in an additional 2 patients by enlargement of the cisterna magna. The extent to which hydrocephalus due to obstruction occurs in this disorder is unclear. Although dilatation of the third and/or lateral ventricles was mentioned in eight patients, only six of them actually required shunting.

It was suggested previously that macrocephaly is one of the principle signs of this disorder [Verloes, 1989]. Although 9 of the 15 patients did have an OFC greater than the 75th centile, only 4 of them had an OFC $\geq$97th centile for chronologic age. Three of those four had hydrocephalus requiring shunting, while the fourth had a Dandy-Walker cyst with hypoplasia of the vermis and some abnormal gyri of the cerebral cortex but was not described as having hydrocephalus. In that six of ten patients, on whom postnatal follow-up data regarding length and OFC are available, have an OFC $>$50th centile for height age, it is reasonable to suggest that the previously reported macrocephaly may be relative and relate in most cases to the postnatal growth deficiency

TABLE I. Review of Previously Reported Cases of 3C Syndrome*

Case number	1	2	3	4	5	6	7	8
Author	Ritscher et al. [1987] patient-1	Ritscher patient-2	Verloes et al. [1989]	Mims and Say [1989]	Guerrieri and Neri [1992]	Hoo et al. [1994] patient-1	Hoo patient-2	Wörle et al. [1994]
Sex	F	F	F	M	M	F	F	F
Performance								
Hypotonia	+	+	+	+	+	NS	NS	+
Gross motor delay	+	+	+	NA	NS	+	+	+
Speech delay	+	+	NA	NA	NA	+	NS	+
Postnatal growth deficiency	+	+	+	NA	NS	+	+	NS
Central nervous system								
"Dandy-Walker malformation/variant"	+	+	NS	NS	+	NS	+	+
Vermis hypoplasia	+	+	−	+	NS	+	+	+
Enlarged 4th ventricle	+	+	+	−	NS	+	+	+
Enlarged cisterna magna	−	+	+	−	NS	+	+	+
Hydrocephalus/enlarged lateral ventricles	+	−	−	−	NS	+	+	−
Craniofacies								
Macrocephaly	+	−	−	−	−	−	−	−
Prominent forehead	+	+	+	+	+	+	+	+
Prominent occiput	+	+	−	+	+	−	−	−
Large anterior fontanelle	+	+	+	NS	NS	+	NS	+
Ocular hypertelorism	+	+	+	+	+	−	−	+
Coloboma	NS	NS	−	−	−	NS	−	+
Depressed nasal bridge	+	+	+	+	−	−	+	+
Downslanting palpebral fissures	+	+	+	−	−	−	+	+
Cleft palate/bifid uvula	+	−	+	+	+	−	−	−
Cardiac defects								
Defects of endocardial cushion	CAVC	PAVC	−	−	Parachute-shaped mitral valve	Cleft mitral valve	−	−
Other cardiac defects	−	−	VSD/ASD	Tetralogy of Fallot	VSD	Single atrium	ASD+PS	VSD
Other	11 pairs of ribs		Absent first ribs	Single umbilical artery	Nail hypoplasia	Syndactyly, short neck, hypoplasia of ribs	Short neck	

Case number Author	9 Quintana et al. [1994]	10 Digilio et al. [1995]	11 Marles et al. [1995] patient IV	12 Marles patient V	13 Marles patient VI	14 Saraiva et al. [1995]	15 Present patient-1	16 Present patient-2	Total
Sex	F	F	F	F	M	F	M	M	M:F=5:11
Performance									
Hypotonia	+	+	NS	NS	NS	NS	+	+	10/10
Gross motor delay	+	+	NA	NA	NS	NA	+	+	9/9
Speech delay	+	+	NA	NA	+	NA	+	+	9/9
Postnatal growth deficiency	NS	+	NA	NA	NS	+	+	+	9/9
Central nervous system									
"Dandy-Walker malformation"/ variant	+	+	−	+	+	+	+	+	12/13
Vermis hypoplasia	+	+	−	−	+	+	+	+	12/15
Enlarged 4th ventricle	NS	−	−	+	−	+	+	+	10/14
Enlarged cisterna magna	NS	+	−	+	−	NS	+	+	9/13
Hydrocephalus/ enlarged lateral ventricles	−	+	−	−	−	+	+	+	8/15
Craniofacies									
Macrocephaly	−	+	−	−	+	+	−	−	3/15
Prominent forehead	−	+	−	−	−	+	+	+	12/16
Prominent occiput	+	−	−	−	−	+	−	−	6/16
Large anterior fontanelle	NS	NS	+	NS	+	+	+	+	10/10
Ocular hypertelorism	+	+	+	+	+	+	−	+	13/16
Coloboma	−	+	+	+	−	−	−	−	4/13
Depressed nasal bridge	NS	−	NS	NS	NS	+	+	−	8/12
Downslanting palpebral fissures	+	+	NS	NS	NS	−	−	+	9/13
Cleft palate/bifid uvula	−	−	−	−	−	−	−	+	5/16
Cardiac defects									
Defects of endocardial cushion	−	CAVC	CAVC	−	−	−	CAVC	Dysplastic tricuspid valve	8/16
Other cardiac defects	DORV/PS	Tetralogy of Fallot	−	DORV	VSD	PS/ASD(II)	−	VSD/ASD	
Others	Hemivertebrae		Short neck, syndactyly, brachydactyly	Proximal thumb	Syndactyly, brachydactyly	Syndactyly, glaucoma, vertebral defects, hypoplastic ribs	Hypospadias, bowel malrotation, nail hypoplasia	Hypospadias, syndactyly	

*Cardinal manifestations of Ritscher-Schinzel (3C) syndrome. +, present; −, absent; NA, not applicable; NS, not stated; CAVC, complete AV canal; PAVC, partial AV canal; VSD, ventricular septal defect; ASD, atrial septal defect; DORV, double outlet right ventricle; PS, pulmonic stenosis.

seen in this disorder. Colobomata were present in four patients, the iris and retina being affected in three and the iris alone in one. An additional patient had optic nerve atrophy. In addition to the five patients with either cleft palate or bifid uvula, six children had a narrow and/or high arched palate which may well be due to a lack of tongue thrust in utero secondary to hypotonia.

With respect to the cardiac defects, eight cases can be categorized as having defects of the endocardial cushion ranging from complete atrioventricular canal defect to much milder defects of the atrioventricular valve such as parachute-shaped mitral valve [Gurrieri and Neri, 1992] and cleft of the mitral valve [Hoo et al., 1994]. Four additional patients had conotruncal defects including a child who had both complete AV canal defects and tetralogy of Fallot [Digilio et al., 1995], a child with tetralogy of Fallot [Mims and Say, 1985], and two children with a double outlet right ventricle [Quintana et al., 1994; Patient V, Marles et al., 1995]. Death occurred prior to age 4 years secondary to cardiac complications in 5 of the 15 patients.

In addition to the two male patients reported herein with hypospadias, Ritscher et al. reported a brother of the original two sisters described with this disorder, who died at birth with multiple malformations including hypospadias, malrotation of the gut, and a large diaphragmatic hernia [1987]. Neither brain nor heart defects were mentioned; thus, it is impossible to determine if that stillborn male had Ritscher-Schinzel syndrome. However, since patient 1 of the present report had hypospadias and malrotation of the gut, it is most likely that the stillborn male described by Ritscher et al. had the same condition. Furthermore, additional defects seen in that stillborn male were described in other patients with Ritscher-Schinzel syndrome. These include syndactyly [Hoo et al., 1994 (patient-1); Marles et al., 1995 (patient-IV and VI); Saraiva et al., 1995; present case-2], and single umbilical artery [Mims and Say, 1989].

Joubert syndrome is the best-known condition of cerebellar hypoplasia. It also includes hypotonia, developmental delay, abnormal breathing, and/or abnormal eye movements. Based on patient 2 of this report who had hyperpneic episodes and abnormal eye movements as well as a patient with Joubert syndrome reported by Squires et al. who had complex cardiac defects and most of the signs of the Ritscher-Schinzel (3C) syndrome [1991], it is clear that overlap exists between these two disorders. Also it is likely that some patients with Dandy-Walker malformation are examples of Ritscher-Schinzel (3C) syndrome. Golden et al. [1987] reviewed five patients with Dandy-Walker malformation and heart defects one of whom on further review has features consistent with Ritscher-Schinzel (3C) syndrome (JA Golden, personal communication, 1995). In addition to the Dandy-Walker malformation, that child, a girl, had a complete AV canal, a left superior vena cava entering into the coronary sinus, a trilobed left lung, a supernumerary incomplete fissure of the right lung, bilateral colobomata, two accessory spleens, and developmental delay. There were incidental ductules reminiscent of Wolffian origin found in the meso-ovarium of one gonad. The ovaries themselves were normal. In a review of 21 autopsy cases of Dandy-Walker malformation, Murray et al. reported on a newborn boy with tetralogy of Fallot, cleft palate, and single umbilical artery (case 21) [Murray et al., 1985]. Olson et al. reported on a newborn girl with Dandy-Walker malformation, heart defects including a common atrium with a single atrioventricular valve, and total anomalous pulmonary venous return, and syndactyly; and Estroff et al., in reviewing prenatally diagnosed cases of Dandy-Walker variant, mentioned a patient who had a VSD and syndactyly (case 10) [1992].

With respect to recurrence risk, within the 14 affected patients summarized in this report, sisters born to unaffected parents were reported by Ritscher et al. [1987] as well as by Marles et al. [1995], suggesting autosomal recessive inheritance as the most likely cause.

Ritscher-Schinzel (3C) syndrome may well be more common than previously has been appreciated. Careful search for the more subtle facial changes of this disorder and coloboma, cleft palate/bifid uvula, short neck, syndactyly, and hypoplasia of the nails is warranted when evaluating children with Dandy-Walker malformation with or without signs of Joubert syndrome. Differentiation of the Ritscher-Schinzel (3C) syndrome is particularly important since the prognosis with respect to intellectual performance may well be far better than is generally predicted for children with the Joubert syndrome.

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